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Clinical and preclinical perspectives on Chemotherapy-Induced Peripheral Neuropathy (CIPN): A review

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Summary

This review provides an update on the current clinical and preclinical understanding of chemotherapy induced peripheral neuropathy (CIPN). The overview of the clinical syndrome, includes a review of its assessment, diagnosis and treatment. CIPN is caused by several widely-used chemotherapeutics including paclitaxel, oxaliplatin, bortezomib. Severe CIPN may require dose reduction, or cessation, of chemotherapy, impacting on patient survival. While CIPN often resolves after chemotherapy, around 30% of patients will have persistent problems, impacting on function and quality of life. Early assessment and diagnosis is important, and we discuss tools developed for this purpose. There are no effective strategies to prevent CIPN, with limited evidence of effective drugs for treating established CIPN. Duloxetine has moderate evidence, with extrapolation from other neuropathic pain states generally being used to direct treatment options for CIPN. The preclinical perspective includes a discussion on the development of clinically-relevant rodent models of CIPN and some of the potentially modifiable mechanisms that have been identified using these models. We focus on the role of mitochondrial dysfunction, oxidative stress, immune cells and changes in ion channels from summary of the latest literature in these areas. Many causal mechanisms of CIPN occur simultaneously and/or can reinforce each other. Thus, combination therapies may well be required for most effective management. More effective treatment of CIPN will require closer links between oncology and pain management clinical teams to ensure CIPN patients are effectively monitored. Furthermore, continued close collaboration between clinical and preclinical research will facilitate the development of novel treatments for CIPN.

Introduction

Neuropathic pain, defined as " *Pain caused by a lesion or disease of the somatosensory nervous system*" is a challenging clinical problem, with up to 8% of the population suffering from moderate to severe pain. [1, 2, 3]. Neuropathic pain may have an even greater impact on patients than other chronic pain syndromes with affected individuals rating their quality of life as "worse than death" , on the EQ-5D, a validated quality of life measure [3]. Unfortunately, many modern chemotherapeutic agents can cause both acute and chronic peripheral neuropathy - chemotherapy induced peripheral neuropathy (CIPN) [4]. During oncological treatment, the severity of the acute syndrome may require reducing the dose of chemotherapy or even stopping it, with potential impact on tumour control and survival.

Chemotherapy-induced painful neuropathy (CIPN) is a major dose-limiting side effect of several first-line chemotherapeutic agents [5-10]. CIPN is a challenging and complex pain syndrome that we have no effective preventive and limited treatment options for currently. CIPN can have a major and prolonged impact on quality of life for patients. As oncological treatments have advanced, cancer survival has increased significantly, with many patients either being cured of cancer or living for many years with cancer. Given the prevalence of the common cancers (e.g. breast, ovarian, colorectal) these chemotherapeutics counteract, CIPN affects several million patients worldwide each year. CIPN also places a significant economic burden on patients due to workloss and the healthcare system due to its prevalence [11]. Effective collaboration between preclinical and clinical researchers is needed to translate improved understanding of the underlying mechanisms into development of effective preventive and treatment strategies [12]. This review aims to provide an overview of the clinical syndrome, its assessment, diagnosis and treatment, and how our improved understanding of underlying mechanisms contribute to this. While there are, multiple factors contributing to CIPN, we will focus on the role of mitochondrial dysfunction, oxidative stress, immune cells and changes in ion channels in CIPN rodent models.

CIPN: The Clinical Syndrome

CIPN usually presents as a typical "glove and stocking" neuropathy. Patients describe a range of predominantly sensory symptoms including numbness, parathesia, ongoing/spontaneous pain, hypersensitivity to mechanical and/or cold stimuli in their hands and feet. In more severe cases, loss of vibration sense and joint position sense contribute to the impact on function. Autonomic and motor dysfunction may also occur. Patients can have significant difficulty in essential daily functions including difficulty in fine finger movement such as buttoning clothing, and unsteady gait (numbness, loss of joint position sense); pain on walking (mechanical hypersensitivity); inability to remove items from a fridge, or exacerbation in cold weather (cold hypersensitivity). CIPN may present acutely, during chemotherapy, such as is commonly seen with platinum based compounds [13]. It may also occur after treatment has finished - a phenomenon known as "coasting" -where either mild neuropathy worsens, or new CIPN develops. This is challenging for oncologists, as there is no indication during chemotherapy to allow dose modification in order to reduce CIPN [14]. Pain and sensory abnormalities can persist for months or years following the cessation of chemotherapy [5, 15, 16]. Therefore, patients may well be cancer-free, but suffering a debilitating neuropathy evoked by their cancer treatment.

Peripheral neuropathy has been long associated with established drugs such as platinum agents (e.g. oxaliplatin), vinca alkaloids (e.g. vincristine), and taxanes (e.g. paclitaxel). However, newer, more targeted drugs, such as bortezomib, eribulin and ixabepilone [4, 17] are also associated with significant incidence of peripheral neuropathy. All of these chemotherapeutics have different mechanisms by which they evoke their anti-mitotic effects e.g. perturbation of microtubule dynamics, DNA cross-linking, proteasome inhibition. Whether all these drugs evoke neurotoxicity by similar mechanisms remains to be determined.

Prevalence and risk factors for CIPN

The prevalence of CIPN varies between different agents, with reported rates varying from 19% to more than 85% [18]. While the agent and dose used is an important determining factor, there is no doubt that the lack of a gold standard agreed assessment tool impacts on reported rates of CIPN [19].

A systemic review and meta-analysis of CIPN incidence and prevalence with paclitaxel, bortezomib, cisplatin, oxaliplatin, vincristine or thalidomide (solo or combination) treatment demonstrated the persistence of this disorder [20]. CIPN was observed in 68.1%, 60%, and 30% of patients, within the first month, at 3 months, and at ≥6 months, respectively, after cessation of chemotherapy, when looking at chemotherapy as a whole. While type of chemotherapy is important, at least part of the variability in reported prevalence was due to differences in the timing of assessment [20].

A number of possible risk factors have been identified, including genetic factors, although there is a need for more systematic evaluation of potential contributory factors. A number of single nucleotide polymorphisms potentially associated with CIPN have been identified through Genome Wide Association Studies. Proteins with a range of functions have been identified, including axon outgrowth, sodium channels and neuronal apoptosis [21-25]. Studies of clinical risk factors are limited, often with small sample sizes. From the available data for CIPN, a history of neuropathy prior to starting chemotherapy (eg diabetic), impaired renal function with reduced creatinine clearance, and a history of smoking may all increase risk of developing CIPN. The cumulative dose of chemotherapy is well recognised as a major risk factor, with growing interest in the effect of levels of circulating growth factors or other biological markers as a means of early identification of quantifiable risk factors [20].

Assessment and diagnosis of CIPN

There is currently no widely accepted, standardized assessment approach for diagnosis of CIPN per se. There are a number of guidelines on assessment and diagnosis of neuropathic pain in general, which may be useful in CIPN [26-28]. Onset of symptoms during, or shortly after, chemotherapy is normally described, often affecting feet first, then with impairment of sensation in fingers and hands. If patients describe abnormalities in sensation, or these are detected on clinical examination, then CIPN should be suspected. Early identification allows treatment decisions about continuation, or not, of chemotherapy to be better informed, as well as allowing initiation of anti-neuropathic agents, if appropriate [29, 30].

Accurate understanding of the epidemiology of CIPN, early identification and treatment of the clinical problem and evaluation of new treatments would all be improved by a standardized approach. The aim of the CI-PeriNomS Study Group was to assess reproducibility and validity of existing measures, and if necessary develop a simple and reproducible assessment for CIPN to try and meet this need [31]. A number of the tools available for assessing CIPN have been robustly assessed and show good reliability and validity (see table 1) [32]. From this, abnormalities in monofilament testing and vibration perception may be useful in identifying CIPN [33-35]. Quantitative sensory testing (QST) is recommended as part of neuropathic pain assessment, and may have clinical utility in early assessment of CIPN. [26, 27]. There is some evidence that there are baseline QST deficits in cancer patients even prior to starting chemotherapy, that may predispose them to developing CIPN, raising the possibility that the cancer process itself may be involved [36]. Sensory abnormalities, for example with raised detection threshold of small bumps of variable quantified sizes ("bumps test"), with an associated reduction in Meissner's Corpuscles counts were found in patients before chemotherapy. Furthermore, long-term outcome for pain and sensory disturbances during chemotherapy was more pronounced in patients with baseline sensory deficits compared to patients who presented without deficits [37, 38].

In patients with established CIPN QST abnormalities indicate deficits in A-beta fibe (altered touch detection to monofilaments, and altered bumps test), A-delta fibre (impaired sharpness detection) and C-fibre (pin prick) function. The importance of these findings is that classes of primary afferent fibers show differential impairments, indicating that the underlying mechanisms are particular to nerve fiber types as opposed to a non-specific toxicity [16, 39, 40]. Changes in QST have been shown to be associated with alterations in epidermal nerve fibre density, occurring in a pattern that matches the distribution of symptoms, such that the lowest counts are in the painful area, but get progressively higher moving proximal where the symptoms change to numbness and then to no complaint. The decrease in ENF density matches the QST data in these patients in that they had elevated pain and sharpness detection thresholds in the fingers and palm [16, 41] . Currently, routine clinical assessment of patients undergoing chemotherapy often does not include measurement of

sensory function. Based on the current evidence, simple tests of vibration sense or light touch may be useful clinical tools, that merit further study.

Prevention and treatment of CIPN

Many RCTs have investigated potential therapies for the prevention of CIPN development or reversal of established CIPN. However, clinical practice guidelines from the American Society of Clinical Oncology (ASCO) following a systematic review of this literature did not recommend any agent for the prevention of CIPN. There have been a number of small trials of agents to prevent CIPN developing, ranging from acteyl-l-carnitine to vitamin E, with no evidence of major benefit [30]. Treatment of CIPN is mainly based on evidence from other chronic neuropathic pain conditions, rather than specifically targeting underlying mechanisms in CIPN. A comprehensive review of the evidence base for all types of neuropathic pain found some overestimation of the treatment effect (~10%), with combined numbers needed to treat (NNTs) being modest (table 2). In the ASCO guidelines, specifically about CIPN, a moderate recommendation was made for duloxetine in the treatment of established CIPN. Generally, whilst evidence for agents used in other neuropathic pain syndromes (as shown in table 2) is lacking for CIPN, it is still reasonable to try them, after appropriate discussion with the patient. There was also a weak recommendation for a topical gel containing baclofen (10mg), amitripyline (40mg) and ketamine (20mg), based on one study [30, 42]. As preventative/curative treatment options for CIPN are currently limited, dose reduction or cessation of chemotherapy is often associated with the emergence of symptoms of neuropathy [43]. Thus, CIPN potentially impacts on both the quality of life and survival of cancer patients. There are a number of areas of therapeutic interest arising from preclinical studies.

Animal models of CIPN

Developing rodent models of CIPN which replicate all the symptoms that patients report is somewhat challenging because numbness, tingling and ongoing pain all rely on verbal report from the patient. Thus, most studies have focussed on measuring evoked pain-like behaviours as has been the case for preclinical studies with other chronic pain models. Investigations into novel measures of

spontaneous pain in CIPN rats are ongoing and paclitaxel-induced deficits in burrowing behaviour and voluntary wheel running were recently observed (data shown at NeupSIG 2017). Rat and mice models of CIPN have been reported following administration of different chemotherapeutics including paclitaxel, docetaxel, vincristine, cisplatin, oxaliplatin, bortezomib [44, 45]. Initial work investigating the neurotoxicity associated with paclitaxel involved direct application of paclitaxel to peripheral nerves resulting in degeneration and specific aggregation of microtubules [46-48]. However, the relevance of such local application of chemotherapy to understanding mechanisms of CIPN that are evoked by systemic administration is limited due to the high endoneurial concentration. In later studies, rodent models of paclitaxel-induced painful neuropathy were developed using systemic paclitaxel administered via intravenous or intraperitoneal routes e.g. [49, 50]. In fact, most of the dosing regimens (reviewed in [44, 45]) utilized to create rodent CIPN models involve intermittent systemic administration to mimic cycles of chemotherapy as opposed to daily dosing.

Typically, most models of CIPN involve the solo administration of a given chemotherapeutic in the absence of tumour load. However, there are reports using a rat model possessing an implanted subcutaneous tumour with combined paclitaxel and cisplatin treatment [51, 52]. Animal health must be considered when employing rodent models of CIPN for ethical reasons and practical feasibility. Pain-like behaviours cannot be accurately assessed if rodents are ill due to systemic toxicity and thus lethargic/unresponsive to hind paw stimulation. Although rodent models of CIPN with a tumour could be considered as more clinically relevant, the practical/ethical issues of this should not to be underestimated. In addition, as chemotherapy is often received after surgical removal of the tumour to eliminate possible micro-metastases, modelling CIPN through chemotherapy administration alone is a valid approach. For new preclinical investigations, the use of established intermittent dosing schedules to generate CIPN models is encouraged as much as possible. Wide adoption of the same dosing schedules across different laboratories would further understanding of causal mechanisms of CIPN and enhance reproducibility.

CIPN models typically display sensory symptoms such as mechanical allodynia, mechanical hyperalgesia, cold allodynia, and in some reports, heat hyperalgesia. tOxaliplatin-induced peripheral neuropathy is associated with an acute cold/mechanical hypersensitivity within hours of administration and a chronic neuropathy. Both syndromes can be replicated in rats and mice at a range of systemic doses [45]. Studies with paclitaxel demonstrated that the cumulative dose administered affects both the integrity of peripheral nerves and the behavioural symptoms evoked. Systemic administration of low-doses of paclitaxel (<10mg/kg cumulative dose) did not markedly affect neural microtubule structure or cause aggregation [53] as observed following epineural administration [46-48]. Following low dose paclitaxel, neurodegeneration was not evident mid-axon or in the DRG [53], however there is a loss of intraepidermal nerve fibres (IENFs) [54, 55]. Greater degrees of degeneration in peripheral nerves and the DRG were caused by larger cumulative doses of paclitaxel (<16mg/kg) in a dose-dependent manner [49, 56-58]. The dose-dependent effects of paclitaxel administration have also been observed in patients, where the incidence and severity of neuropathic signs and symptoms increased relative to increasing cumulative doses of paclitaxel [59]. Paclitaxel-evoked behaviours in rodents are also dose-dependent. Mechanical and cold allodynia without motor deficit are observed at low doses [50, 60, 61]. In contrast, heat hypoalgesia and motor deficit is reported at high doses, which is likely indicative of significant neurodegeneration [49, 62-64]. Collectively, these studies indicate that pain associated with CIPN is not necessarily a result of marked peripheral nerve degeneration.

Role of mitochondrial dysfunction in CIPN

Over the last decade, research has identified mitochondrial dysfunction has a significant contributory factor in CIPN. The first preclinical evidence identified swollen and vacuolated mitochondria in both myelinated axons and C-fibres in peripheral sensory nerves following systemic paclitaxel [53]. Paclitaxel-induced changes in neuronal mitochondria, correlated to the development and maintenance of paclitaxel-induced pain syndrome i.e. present prior to and during paclitaxel-induced pain, but absent when the pain syndrome had resolved [53]. These low dose paclitaxel-induced mitochondrial changes in C-fibres and myelinated axons have since been confirmed by many groups

[65-70]. Paclitaxel increased the incidence of swollen/vacuolated mitochondria in dorsal root C-fibres and A-fibres [66] and the DRG [70-72], but not in the ventral root or Schwann cells [66]. There is also evidence for mitochondrial dysfunction from the clinical literature. Two case reports show electron micrographs of sensory axons containing swollen, vacuolated mitochondria in sural nerve biopsies from patients with chemotherapy-induced neuropathy evoked by paclitaxel [73] and docetaxel [74]. Swollen/vacuolated mitochondria have also been observed in C-fibres and A-fibres of rat models of oxaliplatin-induced painful neuropathy [75] and bortezomib-induced painful neuropathy [76]. The presence of swollen mitochondria does not indicate the nature of mitochondrial dysfunction evoked. This can be determined through assays of mitochondrial function. Significant decreases in complex I-stimulated and complex II-stimulated respiration in sciatic nerves from paclitaxel-, oxaliplatin and bortezomib-treated rats were observed prior to, and during chemotherapy-induced pain behaviour [76, 77]. Recent data discussed at NeupSIG 2017 demonstrates the maximal respiration and spare reserve capacity (the respiratory ability of the cell to overcome stress) were significantly decreased in DRG neurons from paclitaxel-treated rats prior to pain onset [78]. During paclitaxel-induced pain, these OXPHOS-driven respiratory deficits in DRG neurons resolved, yet DRG neurons become more glycolytic in their function and preferentially switch to glycolysis from OXPHOS. The switch to glycolysis may be an adaptive mechanism to produce less ROS and prevent apoptosis through the increased pentose phosphate pathway activity and elevated glutathione peroxidase levels [79]. These paclitaxel-evoked changes in bioenergetics are also associated with decreased ATP. Prior to and during paclitaxel-induced pain, less ATP was present in DRG neurons *in situ* [78], yet deficits in ATP production in peripheral nerves are only observed during maximally stimulated conditions [77, 80]. There was no change in the bioenergetic status of DRG neurons of paclitaxel-treated rats when the pain syndrome had resolved [78] further indicating the contribution of these factors to the development and maintenance of paclitaxel-induced pain.

Several studies have examined in vivo pharmacological modulation of the mitochondrial electron transport chain (ETC) in CIPN models [81-83]. Differential effects of specific complex inhibition have been observed (reviewed in [84]) which may be explained by route of drug administration, inhibitor in

question or time point examined post chemotherapy administration. For example, antimycin A (complex III inhibitor) significantly inhibited the development of paclitaxel-induced mechanical hypersensitivity when given before and during paclitaxel administration, but had no effect when given after paclitaxel administration [83]. Other pharmacological reagents that directly interact with mitochondria and their function in different ways have shown their potential to alleviate CIPN [53, 69, 70, 85-87]. Acetyl-L-carnitine (ALC) is involved in free fatty acid oxidation and acts as an antioxidant. Prophylactic ALC administration prevented the development of paclitaxel-induced mechanical hypersensitivity [53]; paclitaxel-evoked increase in swollen/vacuolated mitochondria in C-fibres [65]; and paclitaxel-, oxaliplatin and bortezomib-evoked compromises in mitochondrial respiration in sciatic nerves [76, 77]. Despite promising preclinical data [88-91] and an open-label phase II trial of CIPN patients [92], a placebo-controlled RCT reported prolonged ALC treatment was associated with more severe paclitaxel-evoked neurotoxicity in breast cancer patients [93]. TRO19622 /Olesoxime, which directly binds to mitochondria (at the mPTP), attenuated chemotherapy-induced mechanical hypersensitivity and IENF loss, but had no effect on paclitaxel-induced spontaneous discharge in C- and A-fibres [85, 86]. Inhibition of mitochondrial fission significantly attenuated oxaliplatin-induced mechanical hyperalgesia [87]. Pifithrin-μ, an inhibitor of mitochondrial p53 accumulation, prevented development of paclitaxel- and cisplatin-induced mechanical hypersensitivity[70]. Pifithrin-μ also prevented paclitaxel-evoked mitochondrial changes in sensory neurons and IENF loss with evidence of enhancement of paclitaxel's anti-tumour effects [70]. Similarly, minoxidil was recently shown to prevent paclitaxel-evoked nociceptive behaviour and mitochondrial changes in sensory neurons accompanied with augmentation of paclitaxel's anti-tumour action [69].

Role of oxidative stress in CIPN

Mitochondria are a major source of reactive oxygen species (ROS) and increased ROS production can be a consequence of mitochondrial dysfunction. However, there are other cellular sources of ROS and reactive nitrogen species (RNS). Evidence for ROS involvement in neuropathic pain dates back to the 1990s e.g. [94] and ROS/RNS have multiple effects on neuronal excitability (reviewed in [95]). The role of oxidative stress in CIPN has been examined *in vivo* using pharmacological reagents that scavenge ROS. PBN, a non-specific ROS scavenger, inhibited the

development of paclitaxel-induced mechanical hypersensitivity [96, 97]; reversed established paclitaxel-induced mechanical & cold hypersensitivities [96, 97]; and bortezomib-induced mechanical hypersensitivity [98]. High doses of TEMPOL, a superoxide dismutase mimetic, inhibited the development and maintenance of paclitaxel-induced mechanical hypersensitivity [97, 99], but was ineffective on cold allodynia [97]. Another SOD mimetic, MnL4, inhibited oxaliplatin-induced mechanical and cold hypersensitivities [100]. Peroxynitrite decomposition catalysts have been shown to reverse established paclitaxel-induced mechanical hypersensitivity [101] and to also prevent the development of mechanical hypersensitivity induced by paclitaxel, oxaliplatin and bortezomib [80, 101]. Novel mitochondria-targeted antioxidants have also been evaluated. SS-31 attenuated oxaliplatin-induced cold & mechanical hypersensitivities [102]. MitoVitE attenuated the development of paclitaxel-induced mechanical hypersensitivity [103].

Other studies have measured ROS/RNS levels within the nociceptive system of CIPN models *in vivo* to understand the cellular basis/location of oxidative stress during CIPN. Increased RNS production was indicated in the spinal cord of paclitaxel-treated rats [101]. In addition, increased ROS and RNS levels were seen in lumbar DRG following chronic oxaliplatin treatment in mice [102]. Data discussed at NeupSIG 2017 showed how oxidative stress is linked to the development, maintenance and resolution of CIPN. ROS levels were elevated in superficial spinal neurons and non-peptidergic (IB4+) DRG neurons, *in vivo*, prior to the onset of paclitaxel-induced pain behaviour [79], suggesting ROS is an initiating factor. The preferential elevation of ROS in IB4+ neurons could suggest a direct mechanism by which TRPA1 channels, known neuronal ROS sensors and predominantly expressed on IB4+ DRG neurons [104], contribute to paclitaxel-induced pain [105, 106]. To understand how ROS was managed endogenously, we also examined the activity of different antioxidant enzymes in the DRG and peripheral sensory nerves during the timecourse of paclitaxel-induced painful neuropathy. Enhanced activity of mitochondrial and cellular endogenous antioxidant enzymes in the DRG and peripheral nerves was observed, however this was inadequate and delayed in its onset leading to excessive ROS in peripheral sensory axons [79]. Others have demonstrated an impaired mitochondrial antioxidant response following paclitaxel,

oxaliplatin and bortezomib [80]. Collectively these *in vivo* preclinical studies suggest that mitochondrial ROS is causal to the development and maintenance of CIPN.

Role of immune cells in CIPN

In addition to effects on mitochondria and the generation of oxidative stress, chemotherapy agents also engage the innate immune system to induce peripheral neuropathy. A key mediator in this is the toll-like receptors (TLR). These are transmembrane proteins that normally function to detect various pathogens, TLR4 specialized to detect bacterial pathogens and TLR3 specialized to detect viral pathogens by example. TLR4 is also activated by several chemotherapeutics[107]. TLR4 and its immediate downstream signals are increased in the DRG of rats with paclitaxel-induced hyperalgesia; and this hyperalgesia can be prevented by co-treating animals with TLR4 antagonists during chemoterapy[108, 109]. Similarly, mice with a genetic knockout of either TLR4 or TLR3 fail to develop hyperalgesia following treatment with cisplatin[110]. It appears that a key result of TLR4 activation by chemotherapeutics is to increase pro-inflammatory cytokine expression in the peripheral and central nervous systems. The C-C motif chemokine ligand 2 (CCL2, also called monocyte chemoattractant protein 1 or MCP1) and its receptor CCR2 are increased small DRG neurons that appear to be nociceptors and in spinal astrocytes in rats with paclitaxel related CIPN. [111]. Gene knockdown or knockout of CCR2 or use of a chemical CCR2 antagonist reduced neuropathic pain in mice[112 113].

Macrophages are normally not found in large numbers in the DRG, yet the immediate result of the paclitaxel-induced increase in CCL2 in the DRG is a marked increase in these cells within the DRG within a few days of treatment[114]. These macrophages have a pro-inflammatory phenotype that results in increased levels of Interleukin-1 (IL-1) and Tumor necrosis factor alpha (TNFα) in the DRG. A number of studies have shown that pro-inflammatory cytokines such as these produce hyperalgesia to both thermal and mechanical stimuli[115, 116]. This occurs by a number of mechanisms. IL-1 and TNFα act on both spinal and DRG neurons to lower their threshold of activation, a process

termed sensitization, and to induce spontaneous discharges[117, 118, 119]. TNFα specifically also suppresses the signalling of spinal GABA neurons leading to central disinhibition of pain signalling [120]. IL-1 and TNFα, as well as IL-6 also increase the release of bradykinin, serotonin, and histamine that further augments pro-inflammatory processes [121, 122]. Increased production and release of IL-1, TNFα and CCL2 is a shared effect following administration of several chemotherapeutics including paclitaxel [123], cisplatin [124] and vincristine[125]. Importantly given that both neurons and glial cells express receptors for these cytokines and can also produce these following activation this mechanism has the potential to become self-sustaining[126].

Increased levels of IL-1, TNFα and CCL2 in the DRG and spinal cord produce alterations in Schwann cells along peripheral axons, satellite cells in the DRG, and astrocytes in the spinal cord that further contribute to chemotherapy related hyperalgesia. A constant observed following treatment with several different chemotherapy agents is that astrocytes show a down-regulation in the expression of glutamate transporters. These are key to clearing synaptically released glutamate and dysfunction in this process leads to hyperexcitability of spinal neurons. As referenced above, the activation of Schwann cells leads to further release cytokines IL-1 and TNFα [127 128, 129] (see more below), but also leads to the extirpation of these cells from peripheral axons [56], resulting in reduced action potential propagation as well as longer term reduced protection and nourishment of nerve fibers. Satellite cells in the DRG react similarly to Schwann cells when exposed to chemotherapy agents[130] resulting in pro-apoptotic stress in DRG neurons. Satellite cells also increase their expression of gap junctions following chemotherapy treatment. Although the exact basis is unclear this appears to further promote pain signalling given that gap junction blockers produce an analgesic effect in CIPN mice [131]. An unusual aspect of glial response in the spinal cord is that astrocytes, but not microglia become activated in CIPN [132, 133, 134]. In many other types of neuropathic pain a primary role is assigned to microglia that does not appear to be involved in CIPN. Like in Schwann cells, inhibitors of gap junctions in astrocytes results in reduced hyperalgesia in CIPN, an a similar anti-hyperalgesic response is produced using the glial inhibitor minocycline [135, 136].

Changes in ion channels in CIPN

The net result of the activation of innate immune responses in the DRG and spinal cord is the induction of hyperexcitability and ectopic spontaneous activity in both peripheral and spinal neurons. These, in turn are due to alterations in neuronal ionic homeostasis as revealed by ion channel microarray [137]. By example, given the primacy of Na^+ ions in generating electrical activity in neurons, it is almost expected that alterations in voltage-gated sodium channels occur in CIPN. Recent work by our group that will be presented at NeuPSIG 2017 shows that the expression and function of the voltage-gated sodium channel Nav1.7 is markedly increased in DRG neurons following paclitaxel treatment and contributes directly to the development of ectopic spontaneous activity in nociceptors (Li et al, 2017, submitted). As well, prolonged opening in voltage-gated Na+ channels is produced by oxalate, a metabolite of oxaliplatin that results in lowered activation threshold and ectopic firing in DRG neurons [138, 139]. Enhanced activity in sodium channels would appear to reflect the increased peripheral axonal excitability seen prior to symptom expression in patients [140, 141]. Beyond the spinal cord and DRG, increased expression of voltage gated sodium channels is also found in forebrain regions following paclitaxel treatment [142]. A caveat to this latter observation is that forebrain changes in sodium channels would be secondary to alterations occurring elsewhere given the poor penetrance of paclitaxel to the CNS. These preclinical observations are supported by clinical findings in that voltage-gated sodium channel blockers, such carbamazepine, that have found success in treating some [143], but not all neuropathic pain patients [144].

A second ion channel that is key in resulting neuronal excitability is that for potassium. Alterations in K+ channel function have been noted at several levels of the neuraxis in CIPN. By example, K+ channels are down-regulated in the cortex and in primary afferent neurons of rats with oxaliplatin CIPN [145, 146]; and in the DRG of rats with paclitaxel-related CIPN [137]. In congruity with the observed changes in Na+ and K+ channels just noted others have reported an increased expression in hyperpolarization-activated channels (HCNs) that are permeable to both ions in CIPN [147]. Mathematical modelling of the consequences of the observed changes in Na+ and K+ channels indicates that these account well for the observed hyper-excitability in nociceptors that occurs in

oxaliplatin CIPN [148]. The therapeutic potential of targeting K+ channels in CIPN is supported by the observation that the K+ channel opener, retigabine, reduced signs of hyperalgesia in mice with cisplatin-related CIPN [149].

Voltage-gated calcium channels are key in regulating synaptic transmission and so not surprisingly also implicated in the hyper-excitability in CIPN. DRG neurons show increased levels of voltage-gated calcium channel mRNA following paclitaxel treatment in mice [150]. Antagonists to voltage-gated calcium channels including gabapentin and ethosuximide were both effective in reducing signs of hyperalgesia in rodents with paclitaxel- and vincristine-induced CIPN[60, 151]. Consistent with these findings is that paclitaxel treatment was shown to alter calcium metabolism in primary afferent fibers [152] and treatment with minoxidil reversed this effect while also ameliorating the behavioural signs of paclitaxel-related CIPN [69].

A large group of non-selective cation channels specifically localized in nociceptors that are involved in CIPN symptoms is the transient receptor potential (TRP) channels. Specifically, the TRP vanilloid 1 (TRPV1) and the TRP ankyrin 1 (TRPA1) subgroups have been implicated in CIPN-related pain. TRPV1, commonly also known as the receptor for capsaicin (the active ingredient in hot chili peppers) is physiologically activated by protons, heat above 42^{o}C, and endogenous lipids produced during inflammation (for review, see[153]). The sensation produced by activation of TPV1 are exactly those that are experienced by CIPN patients[16, 41], in cutaneous nociceptors TRPV1 produces burning[154], while in deep tissue nociceptors TRPV1 produces deep aching pain [155, 156]. Paclitaxel activates and sensitizes the function of TRPV1 and TRPV1 antagonists produce analgesia in paclitaxel-related CIPN [157]. Similarly treatment with either bortezomib or cisplatin produced an increases in TRPV1 expression in DRG and spinal cord in mice [158, 159]. Paclitaxel directly interacts with the TRPV1 channel to produce both and acute facilitation of signalling and also produces a long-term alteration of channel desensitization. The acute interaction has also been validated in human DRG neurons [160]. Parallel studies suggest that

oxaliplatin also sensitizes the TRPV1 and that this effect is mediated by the G-protein coupled receptor G2A [161].

TRP ankyrin 1 (TRPA1) is often colocalized with TRPV1 and is activated by formalin, allyl isothiocyanate, and acrolein; and by temperatures below 17^0C [162]. Given that activation of TRPA1 is activated by noxious cold stimuli in animals[163], it has been suggested that this channel may mediate the acute hypersensitivity to cold observed in patients following oxaliplatin treatment. Preclinical studies using oxaliplatin appear to support this view[164, 165] and appear to also be generalizable to paclitaxel-induced cold hyperalgesia [105]. Preclinical studies have further detailed that chronic symptoms of CIPN may be mediated by chemotherapy-induced activation of proteinase-activated receptors (PARs) that activate phospholipase C, protein kinase A and protein kinase C epsilon that then sensitize TRPA1 as well as TRPV1 and TRPV4 channels, respectively [106]. Further support for a role of TRPA1 in CIPN is that receptor deficient mice were shown to be resistant to both oxaliplatin- and bortezomib-related CIPN[167]. Interestingly, in the context of previous discussion on oxidative stress, TRPA1 mediates neuropathic pain in trigeminal neurons downstream to the activation of macrophages/monocytes and their generation of oxidative stress [168]. Yet, human psychophysical studies suggest that even though noxious cold activates TRPA1 in rodents this may not be true in humans[166], indicating that perhaps one final TRP channel may have an important role.

The transient receptor potential melastatin 8 (TRPM8) channel is activated by mild cool stimuli between 25 and 28^{o}C and chemically by menthol [169] and has been implicated as analgesic when activated in some nerve injury models [170]. Some have suggested that TRPM8 could mediate cold-hyperalgesia in humans in CIPN. Yet, others have shown that topical menthol produces analgesia in paclitaxel CIPN patients [171] and this has been supported in a recent proof-of-concept study [172]. Other receptors subtypes including A3 adenosine receptors [173], 5HT2A receptors [174, 175], sigma-1 receptors[68] and mGluR5 receptors [176] have been implicated in CIPN and could prove potential avenues for new treatments.

Conclusions

Preclinical models of CIPN can provide vital insight into the neurotoxic mechanisms that initiate and maintain CIPN. Compared to other chronic pain conditions, differential analgesic effects are observed in both CIPN patients and rodent models suggesting different causal mechanisms for CIPN. Many of the causal mechanisms of CIPN described in this review occur simultaneously and/or can reinforce each other. It seems likely therefore, that effective future developments may use combination therapies to either prevent development of CIPN where possible, or direct effective treatment for CIPN. There are very few clinical trials of combination therapies in any type of neuropathic pain, and it may be that to detect a clinically significant effect, we need to reconsider how clinical trials for neuropathic pain are designed [177-179]. An additional complexity in trials of CIPN is the effect of cancer on the pathophysiology of the pain systems: we do need to address how to translate preclinical models of single morbidities (such as CIPN) to the often complex co-morbidities that are seen in our aging population. More effective treatment of CIPN will require closer links between oncology and pain management clinical teams to ensure CIPN patients are effectively monitored. Furthermore, continued close collaboration between clinical and preclinical research will facilitate the development of novel treatments for CIPN.

Figure Legends

Figure 1: Summary of the pathophysiological events contributing to chemotherapy-induced peripheral neuropathy (CIPN) as highlighted in this review. The most common agents provoking CIPN are shown in the bubble in A and the sites of action for these compounds are indicated by the arrows. The structures are also labeled in A while in B the changes occurring in these structures with CIPN are summarized. Reproduced with permission from Boyette-Davis JA, Walters ET, Dougherty PM, Mechanisms involved in the development of chemotherapy induced peripheral neuropathy. Pain Manag. 5 (4): 285-296, 2015.

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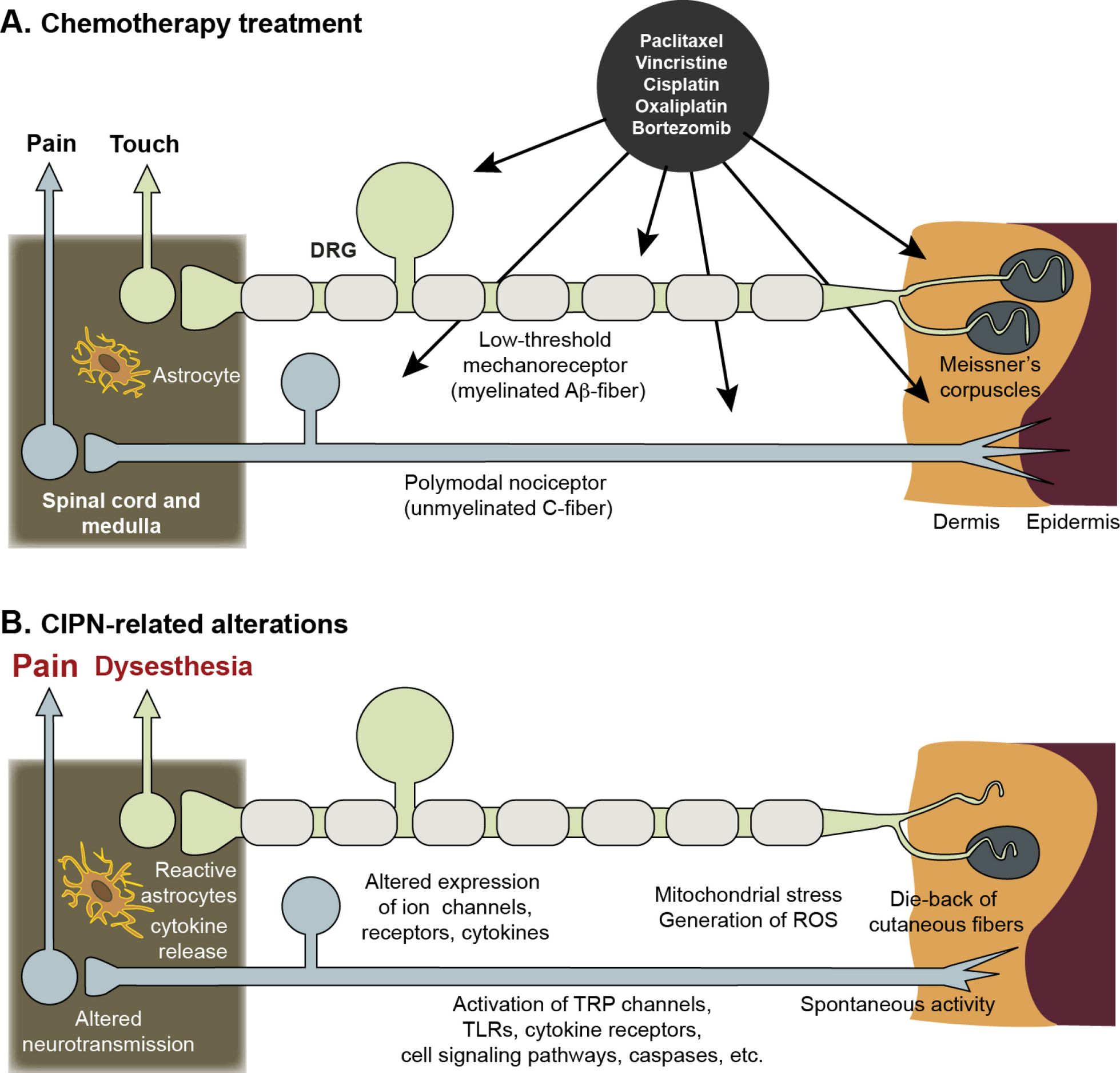
A. Chemotherapy treatment
Paclitaxel
Vincristine
Cisplatin
Oxaliplatin
Bortezomib
Pain
Touch
DRG
Astrocyte
Low-threshold
mechanoreceptor
(myelinated Aβ-fiber)
Meissner's
corpuscles
Spinal cord and
medulla
Polymodal nociceptor
(unmyelinated C-fiber)
Dermis
Epidermis
B. CIPN-related alterations
Pain
Dysesthesia
Reactive
astrocytes
cytokine
release
Altered expression
of ion channels,
receptors, cytokines
Mitochondrial stress
Generation of ROS
Die-back of
cutaneous fibers
Altered
neurotransmission
Activation of TRP channels,
TLRs, cytokine receptors,
cell signaling pathways, caspases, etc.
Spontaneous activity

Table 1: Some of the tools used for assessing CIPN

Tool	Comments	References
National Cancer Institute-Common Toxicity Criteria (NCI-CTC)	Grade 0-3 depending on degree of sensory loss; deep tendon reflexes; parathesia	180, 181
Total Neuropathy Score clinical version (TNSc)	Includes assessment of neuropathy signs and symptoms, with limited information about pain; some quantitative sensory testing (vibration threshold, standardized monofilaments)	182
modified Inflammatory Neuropathy Cause and Treatment (INCAT) group sensory sumscore (mISS)	Includes vibration threshold, standardized monofilaments, plus 2 point discrimination	183
European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30	Not specific for CIPN, but gives a reliable measure of the impact of CIPN, and can allow comparison with other cancer populations.	184
CIPN20 quality-of-life measures	Assesses different components, including sensory, autonomic and motor symptoms;	185, 186

Table 2. Combined NNTs for agents used in treatment of neuropathic pain (based on results from [187]). NNT = number-needed-to-treat; CI= confidence interval; SNRI= serotonin, noradrenaline reuptake inhibitor

Drug	**NNT (95% CI)**	**Strength of recommendation for use**
SNRIs (mainly Duloxetine)	6.4 (5.2-8.4)	Strong, first line
Pregabalin	7.7 (6.5-9.4)	
Gabapentin	7.2 (5.9-9.21)	
Tri-cyclic anti-depressants	3.6 (3.0-4.4)	
Lidocaine patches 5%	Low quality evidence	Weak, second line
Capsaicin patch 8%	10.6 (7.4-19.0)	
Tramadol	4.7 (3.6-6.7)	
Strong opioids	4.3 (3.4-5.8)	Weak, third line
Botulinum toxin A	Only very small studies	Weak, third line, specialist use only